

REMARKS/ARGUMENTS

Claims 15 to 18 and claims 52 to 62 remain in this application.

The Examiner has rejected claim 15 under 35 U.S.C. 102(b) as being anticipated by Ali (DE 196 47 100). The Examiner has also rejected claims 15 to 18 and 52 to 62 under 35 U.S.C. 103(a) as being unpatentable over Ali (DE 196 47 100) in view of Weiner et al (WO 86/0014; IDS citation M1), SaNogueira Jr. et al. (US 6,001,377), Murad (5,804,168) and Cohen et al. (U.S. 5,875,736) and further in view of Raab (IDS citation N10).

The Applicant respectfully submits that claims 15 to 18 and 52 to 62 are patentable over the prior art noted above as cited by the Examiner. Ali, Weiner et al and SaNogueira et al all teach topical compositions comprising urea, in which urea acts as a moisturizer. Ali teaches a moisturizing salve comprising urea, and a procedure for preparing the salve. Weiner et al teaches a topical urea composition for preventing skin damage due to ultraviolet radiation, in which urea acts as a neutralizer of damaging active chemical entities. SaNogueira Jr. et al teaches a topical composition for covering skin imperfections which comprises a skin conditioning component which is selected from a group of compounds including urea. In SaNogueira Jr et al, the skin conditioning component is "useful for lubricating the skin, increasing the smoothness and suppleness of the skin, preventing or relieving dryness of the skin, hydrating the skin, and/or protecting the skin". As taught by SaNogueira Jr. et al, urea is used as a skin moisturizer, similar to Ali.

The final two references cited by the Examiner, Murad and Cohen, teach topical compositions comprising skin protectants including various combinations of anti-oxidants. The compositions claimed by Murad and Cohen do not include urea. The Applicant notes that the present application does not claim compositions for protecting the skin which comprise anti-oxidants alone. Moreover, Murad and Cohen do not teach a method for enhancing the penetration of anti-oxidants through the skin comprising application of a composition comprising urea.

The Applicant respectfully submits that claims 15 to 18 and 52 to 62 are directed to *methods of enhancing delivery of an anti-oxidant to the viable epidermis*, the method comprising the step of applying to the skin surface a composition comprising urea at a given percentage by weight of the composition. The Applicant is aware of compositions in the prior art which comprise urea and one or more anti-oxidants including vitamin E, as disclosed in the references cited in the Examiner's report. However, it has *not* been previously disclosed or suggested that the use of urea in concentrations above 10% w/w enhances the penetration of an anti-oxidant, including vitamin E, through the stratum corneum to reach the viable epidermis.

The top-most layer of the skin, the stratum corneum, consists of keratinized dead skin cells which are constantly being generated from the viable epidermis. The viable epidermis contains the actively dividing dermal cells. Persons skilled in the art will

appreciate that in order to treat various skin disorders, it is necessary to deliver active ingredients to the epidermis where they will be most effective. However, the stratum corneum is an effective barrier against the outside environment. Overcoming this barrier in order to deliver active ingredients such as anti-oxidants and nutrients to the viable epidermis is a problem which is solved by the method disclosed herein. Moreover, the prior art teaches away from the recited subject matter of the present invention, namely that urea *increases* the barrier function of the skin by binding water (Raab, IDS citation N10; Lodén, IDS citation N7), which is contrary to the evidence provided on pages 18 to 20 of the disclosure.

Urea is a component of the skin's natural moisturizing factor and acts as a moisturizer as it binds water (Raab, IDS citation N10). However, the Applicant notes that by binding water, this renders the outer layer of the skin, the stratum corneum, less permeable, particularly to hydrophobic compounds such as vitamin E. None of the above references teach or suggest that urea enhances the penetration of vitamin E through the stratum corneum to the lower levels of the skin. According to the above references, urea would be seen to inhibit the penetration of hydrophobic compounds such as vitamin E.

In support thereof, Lodén (IDS citation N7) states in the introduction, "several studies have shown that urea can increase skin permeability by acting as an efficient accelerant for the penetration of a number of substances". However, Lodén also states that not all studies support the general belief that urea is an effective penetration enhancer. This effect of urea has been demonstrated for the penetration of water in studies on dry and ichthyotic skin where TEWL (transepidermal water loss) was found to be decreased after treatment with urea-containing moisturizers" (see column 2, page 104 of Lodén). Based on the results of studies with 5% and 10% urea (composition C, D and E), the authors concluded that topically applied urea leads to improved barrier function, although where urea exerted its effect was not known (see page 106 of Lodén).

There thus appears to be no generally accepted teaching in the art as to the effect urea has on the penetration of other components into the skin, and Lodén indicates that urea up to 10% concentration improves the barrier function of the skin. Therefore, the Applicant's invention has not been disclosed nor is it obvious based on the teachings in the art cited by the Examiner.

There have been no specific examples in the prior art showing high concentrations of urea, above 10% w/w, enhance the penetration of a high molecular weight oil soluble compound such as Vitamin E to the viable epidermis. In particular, the references cited by the Examiner do not teach that urea enhances penetration of an antioxidant including vitamin E to the viable epidermis.

The Applicant has shown that urea enhances the delivery of anti-oxidants including Vitamin E to the viable epidermis, as shown in the *in vitro* and *in vivo* analyses of skin samples, described on pages 18 to 20 of the disclosure. Vitamin E was chosen as the active compound, as it is known to have a very slow rate of penetration into the skin when applied alone. The HPLC analysis, on pages 19 to 20 of the disclosure, clearly

shows that urea enhances the penetration of vitamin E through the stratum corneum to the lower levels of the skin.

In view of the above statements, the Applicant respectfully submits that the method recited in claims 15 to 18 and 52 to 62 are not obvious in view of the cited prior art.

The priority document of this application is PCT/CA00/01031. A copy of Form PCT/IB/308 for PCT/CA00/01031, dated March 15, 2001, is enclosed to indicate that the International Bureau has provided this international application to the U.S. Patent and Trademark Office (see paragraph 1).

In view of the foregoing election and amendments, the Applicant submits that the claims pending in this case are presently in a condition for allowance. Therefore, the Applicant requests early and favourable disposition of this application.

The Applicant is of the view that no fee is required. The Commissioner is requested to charge any other fee, which may be required for the papers being filed with this letter to Account No. 02-2553.

Respectfully submitted,

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Attachment

PATENT COOPERATION TREATY

WO 01/17484
PCT/CA00/01031

PCT

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

HUNT, John, C.
Blake, Cassels & Graydon LLP
Box 25, Commerce Court West
Toronto, Ontario M5L 1A9
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IMPORTANT NOTICE

Date of mailing (day/month/year) 15 March 2001 (15.03.01)			
Applicant's or agent's file reference 50586/00020			
International application No. PCT/CA00/01031	International filing date (day/month/year) 07 September 2000 (07.09.00)	Priority date (day/month/year) 07 September 1999 (07.09.99)	
Applicant D.T.R. DERMAL THERAPY RESEARCH INC. et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 15 March 2001 (15.03.01) under No. WO 01/17484

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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Form PCT/IB/308 (July 1996)

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